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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,803	01/14/2004	James McSwiggen	SIR-MIS-00001-US-CIP[4]	5421

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
01/24/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/757,803	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 December 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *18-20 and 33-49*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/AMY BOWMAN/
Primary Examiner, Art Unit 1635

Continuation of 11. does NOT place the application in condition for allowance because: Applicant argues the rejection under 35 USC 103(a) and argues that Elbashir et al. teaches away from modifying beyond the 3' nucleotides. Applicant continues to argue the interpretation of the Elbashir et al. reference. However, the instant claims require a total of 10 pyrimidines between the sense and antisense strand to be modified (diminimus of the claim), which is an extension of one nucleotide on each 3' end being modified when compared to Elbashir et al., wherein the board agreed that Elbashir et al. is silent as to data between 19% modification of the duplex and 100% modification of one or both strands.
It is noted that the interpretation of the Elbashir et al. (Tuschl) reference is argued in detail by applicant. However, the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection.
On page 27 of the decision, the board sets forth that appellant's argument that Tuschl teaches avoiding any 2'-O-methyl modifications is unpersuasive and misstates the teachings of Tuschl. A fair reading is that more extensive 2'-deoxy or 2'-O-methyl modification beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi. Stating that complete substitution abolished RNAi is not the same of stating that any 2'-O-methyl modification should be avoided. It is noted that when incorporating chemical modifications into nucleic acid inhibitory molecules, it is routine to balance stability and activity. Therefore, it is a matter of routine optimization to determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active.
The decision also sets forth that nucleic acid molecules are known to be degraded or hydrolyzed by nucleases in vivo and in culture systems and thus it is routine in the art to modify nucleic acids to resist nuclease hydrolysis, and particularly to modify with modifications that were known to enhance stability. Similarly, capping as disclosed by Matulic-Adamic et al. would be reasonably expected to sterically interfere with the active site of a nuclease (see page 25 of decision, for example).
Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.
Importantly, the instant claims are not directed to any specific target sequence and only require 10 pyrimidine modifications collectively between both strands. Therefore, depending on the target sequence, the diminimus of the instant claim breadth is only a difference between one modification on each strand because Elbashir et al. teaches the incorporation of 8 modified positions. Therefore, although applicant continues to argue that Elbashir et al. teaches away, this simply is not the case.
The only modified duplexes that exhibit abolished activity in the Elbashir et al. reference are 100% modified. Elbashir et al. is evidence that incorporation of such chemical modifications into siRNA molecules results in active molecules in some configurations and inactive molecules in others, supporting that routine optimization is needed. Furthermore, Elbashir et al. is evidence that modification is well tolerated in the terminal portions of the duplex, offering further motivation to modify the terminal regions. Elbashir et al. teaches that some modification does not affect RNAi, but helps to reduce the cost of RNA synthesis and may enhance RNase resistance of siRNA duplexes (see page 6885, column 1). Applicant argues that Elbashir only succeeded at modifying a single terminal region on each strand. Importantly, this is all that Elbashir et al. tested and therefore does not teach away from incorporating terminal modifications at the other end. Since the modifications were tolerated on the one end, one would have been motivated to incorporate them on the other end. Again, applicant is not claiming any specific configuration of modifications, but is rather claiming a genus of modification types or combinations thereof at various positions depending on the target sequence.
Applicant continues to argue the teachings of this reference via drawing their own conclusions as to results between the 19% successful modification and 100% unsuccessful modification of Elbashir et al., experiments that simply are not addressed via Elbashir. Applicant points to page 6885 of Elbashir et al. and interprets the passage as teaching away from producing extensively modified duplexes. This passage is interpreted by both the examiner and the board as referring to the only extensive modification that is taught by Elbashir et al., which is 100% modification. Elbashir et al. is completely silent as to modification between 8/42 positions that was successful and 100% modification with a single type of modification that was unsuccessful.
It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; and the instant claims require a total of 10 modifications out of a possible 24 positions. Applicant continues to broadly argue "extensive" modification, rather than directing the arguments to the instant claim scope.
Applicant points to KSR International Co. v. Teleflex Inc. (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by Elbashir et al.
In view of KSR International Co. v. Teleflex Inc., when a combination of admittedly old elements produces a new and beneficial result never attained before, it is evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.
The mere selection of elements from various prior art references and combining them together with no new function is an obvious use of common sense by one skilled in the art and therefore not patentable.
One of skill in the art would reasonably expect for the modifications of Matulic-Adamic et al. to likely benefit the molecules of Elbashir et al. as well. As explained above, the motivation need not be the same motivation set forth by applicant, but rather the motivation to enhance the stability of the molecules as set forth by Matulic-Adamic et al. Elbashir et al. teaches that preferred molecules are modified in the 3'

terminal regions. Therefore, one would reasonably expect for the terminal cap moieties of Matulic-Adamic et al. to enhance the stability of the molecules of Elbashir et al. as well.

It is noted that the only position specific modification that is instantly claimed are terminal caps, which by nature are located in terminal positions. It was known and routine in the art to incorporate terminal cap moieties into nucleic acid inhibitory molecules, as set forth in the instant rejection. Regarding types of nucleotides, there is a finite number of choices for the modifications of the prior art to be incorporated at, purines or pyrimidines. It is certainly within the realm of routine optimization/design choice to incorporate the modifications at a purine or a pyrimidine, given that there are only two choices. Furthermore, the claims are not directed to any specific pattern of modification that has demonstrated any unexpected property, given that the claims embrace combinations of modifications at different positions depending on the target sequence. The quantity of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; and the instant claims require a total of 10 modifications out of a possible 24 positions. Applicant continues to broadly argue "extensive" modification, rather than directing the arguments to the instant claim scope.